Harry L. Arnold Jr. MD Case of the Month

Gradual Loss of IgG Antibodies Against GB Virus C/Hepatitis G Virus in a Patient With AIDS

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GB virus C/hepatitis G virus (GBV-C/HGV) is a positive-sense, single-stranded RNA virus belonging to the family Flaviviridae *and is distantly related to hepatitis C virus (HCV).[1-3] GBV-C/HGV can be transmitted by the parenteral and the sexual route.[1, 4] Among individuals infected with human immunodeficiency virus type 1 (HIV-1) by the sexual route, we and others have demonstrated a high prevalence of GBV-C/HGV infection.[5-8] Recently, Woolley and colleagues reported that AIDS patients co-infected with GBV-C/HGV had a significantly lower mean CD4 cell count than AIDS patients without GBV-C/HGV infection,[9] suggesting that GBV-C/HGV antibody may be lost with progression to AIDS. To our knowledge no data are available on the loss of antibody against GBV-C/HGV in AIDS patients. We now report on an HIV-infected patient who exhibited gradual loss of IgG antibodies against GBV-C/HGV, as well as HCV, with progression of HIV disease.*

Case Report

A 35-year-old Caucasian woman, presumed to have been infected by injection drug use (IDU) with HIV subtype B in 1994, was first seen in October 1995 in our Women's Clinic, which provides medical and psychosocial services to HIV-infected women. At the initial visit, CD4 and CD8 counts were 197 and 435 X 10^6 cells/L, respectively. Plasma was negative for GBV-C/HGV and HCV RNA, as determined by reverse transcription-polymerase chain reaction (RT-PCR) using oligonucleotide primers spanning 377-bp and 257-bp of the 5'-untranslated region of GBV-C/HGV and HCV, respectively.[8] However, plasma was positive for IgG antibodies against GBV-C/HGV and HCV, as measured by enzyme-linked immunosorbent assay (ELISA), with optical density (OD) readings of 1.14 and 2.60, respectively. Hepatitis B virus surface antigen and core antibody were also detected, and liver enzyme levels were abnormal: alanine aminotransferase, 71 IU/L; aspartate transaminase, 118 IU/L; gamma glutamyl transferase, 73 IU/L; and alkaline phosphatase, 294 IU/L. Low-grade squamous intraepithelial lesion (SIL) found on initial visit progressed to high-grade SIL in April 1997, and human papillomavirus 18 was detected by PCR in cervicovaginal lavage cells.

In April 1996, she was diagnosed with *Mycobacterium avium* complex and esophageal candidiasis, and in August 1996, HIV RNA burden was 230,290 copies/mL (Amplicor HIV-1 Monitor Test, Roche Diagnostic System, Somerville, NJ) with CD4 and CD8 counts of 48 and 145 X 10^6 cells/L, respectively. In October 1996, highly active antiretroviral therapy (HAART) was started with the addition of Indinavir to D4T and 3TC. The patient was noncompliant to HAART and in February 1997, cytomegalovirus-associated retinitis was diagnosed in her right eye. A month later, HIV RNA burden was 152,967 copies/mL with CD4 count of 26 X 10^6 cells/L. In April 1997, with increasing compliance to HAART, her HIV plasma viral RNA decreased to 27,334 copies/mL, with CD4 and CD8 counts of 160 and 217 X 10^6 cells/L, respectively. HIV RNA viral load was 230,000 copies/mL in September 1997. In October 1997, non-Hodgkin's lymphoma and HIV-associated myelopathy were diagnosed with a CD4 count of 22 X 10^6 cells/L, after which her health deteriorated rapidly, and she died in January 1998. At autopsy, blood and peritoneal fluid were collected.

Plasma collected over a 27-month period were tested in triplicate by ELISA for IgG antibodies against GBV-C/HGV (Ortho HGV CHOe2 ELISA Test System, Ortho Clinical Diagnostics, Raritan, NJ), HCV (Ortho HCV Version 3.0 ELISA Test System, Ortho Clinical Diagnostics) and HIV (Genetic Systems HIV-1/2 EIA, Genetic Systems Corp., Redmond, WA). In addition, plasma were assayed for reactivity to HIV proteins by Western blot analysis (HIV-1 Western Blot Kit, Cambridge Biotech Corp., Rockville, MD). To assure comparability, all plasma specimens were tested by the above-mentioned assays at the same time. As seen in Fig. 1, the patient lost IgG antibodies against GBV-C/HGV and HCV (positive cutoff value, OD 0.6) between 18 to 20 months after the initial visit, and the OD readings were 0.07 and 0.03, respectively, in the plasma sample collected at autopsy.

Discussion

As a result of HIV-1-induced severe immunosuppression, depressed humoral and cellular immunity has been documented to specific parasitic,[10-12] bacterial[13-14] and viral[11, 15-16] agents. Significantly lower levels of IgG, IgM and IgA antibodies to *Giardia lamblia* were demonstrated in AIDS patients with acute giardiasis.[12] Loss of humoral immune response to *Pneumocystis carinii* in AIDS patients when compared to other immunosuppressed patients or immunocompetent controls has been documented.[13, 17] Moreover,

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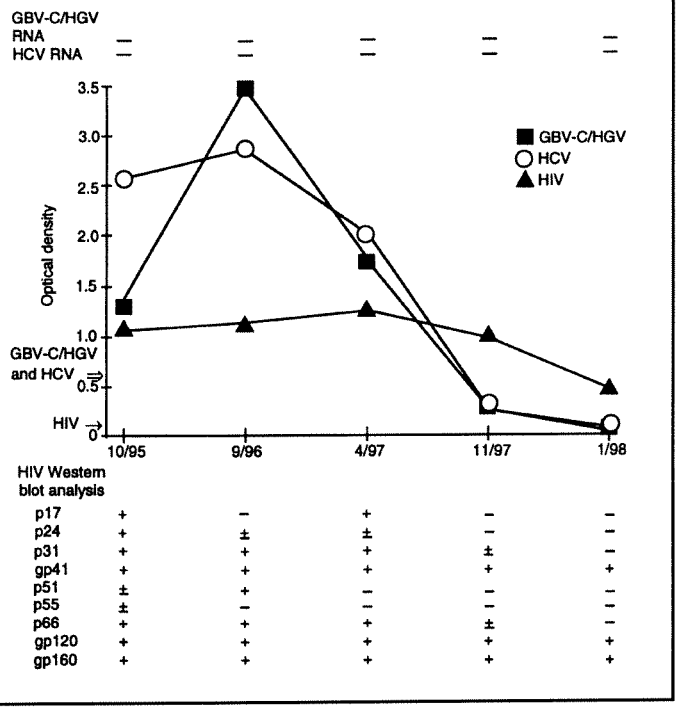
Fig. 1.— Longitudinal analysis of IgG antibody response to GBV-C/HGV, HCV and HIV, as measured by ELISA and Western blot in an AIDS patient. Reactivity to HIV proteins is indicated: positive, +; negative -; indeterminate, ±. ELISA cutoffs were OD 0.6 (⇒) for GBV-C/HGV and HCV, and OD 0.2 (→) for HIV.



progressive loss of IgG antibodies against *Chlamydia pneumoniae* has been demonstrated in middle to advanced stages of HIV-1 infection.[14]

In a study of 95 HIV-1-infected individuals (45 asymptomatic and 40 with AIDS), Radkowski and coworkers[11] demonstrated lower antibody titers to hepatitis B surface antigen, rubella virus and cytomegalovirus in AIDS patients when compared to asymptomatically infected individuals. Similarly, a population-based study of measles and measles immunization in HIV-1-infected children demonstrated loss of anti-measles antibody over time in older children and a statistically significant correlation between lower CD4 counts and measles-mumps-rubella vaccine nonresponsiveness.[16] Finally, time-dependent HCV seroreversion has been reported in a cohort of HIV-1-infected IDU.[15]

Loss of seroreactivity to specific HIV-1 epitopes has also been reported. Up to a 100-fold greater affinity to HIV-1-specific p24 and p17 proteins has been found in asymptomatic HIV-1-infected individuals than in AIDS patients,[18] suggesting that those who develop AIDS either lose or fail to develop high-affinity antibodies early in the infection. These data also demonstrate that the presence of low-affinity antibody and the progressive reduction in titer of specific antibodies are better predictors of disease onset than CD4 cell count. Moreover, antibodies against HIV-1 p24 is undetectable in 45% of individuals by the time of AIDS diagnosis.[19] Although the patient reported here did not exhibit a dramatic drop in IgG antibodies to HIV-1 as measured by ELISA, during the last 3 months before death, there was a gradual loss of reactivity to HIV-1 *gag*-encoded proteins, as determined by Western blot analysis (Fig. 1).

In conclusion, as seen in other opportunistic infections associated with AIDS, AIDS patients co-infected with GBV-C/HGV may similarly lose anti-GBV-C/HGV antibodies during progression to AIDS.

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